REMARKS/ARGUMENTS

Claims 1-4, 8 and 9 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,132,409 ("Felder") in view of either one of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). The claims have not been amended. Reconsideration is respectfully requested.

Claims 1, 5, 6, 8 and 9 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 5,545,396 ("Albert") in view of either one of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). The claims have not been amended. Reconsideration is respectfully requested.

In addition, claims 1, 5 and 7-9 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 6,466,814 ("Ardenkjaer-Larsen") in view of either one of DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). The claims have not been amended. Reconsideration is respectfully requested.

Again, the present invention is directed to a silica-coated vial containing a specific type of diagnostic agent. "Diagnostic agent" is a term defined in the present application in the first full paragraph of page 4. Moreover, claim 1 further restrictively recites that the diagnostic agent claimed is either a non-radioactive metal complex or a hyperpolarized material. These are essential features of the present claims, leading to a specific [vial + agent] combination which applicants contend is very different to the teaching of Schott,

where "diagnostic agent" is not described further (see below). The Examiner is therefore incorrect to equate the use of the term in this application and in Schott Glaswerke.

Felder teaches a plurality of macrocyclic chelating agents and chelates thereof. In several examples, Felder discloses that the solution may be diluted and put into vials. Felder, however, neither discloses the material of the vials nor discusses any specifics of the vials let alone claims a vial.

Schott Glaswerke teaches a silica-coated vial for use with pharmaceuticals or diagnostic agents. Schott Glaswerke provides no further description of the contained material other than this generic reference to 'pharmaceuticals' or 'diagnostic agents'.

Walther discloses a glass tube with an oxide coating. Walther notes that the prior art taught a silica-coated tube for use with (generically) pharmaceuticals. Walther contains no reference to diagnostic agents or contrast agents per se.

Ardenkjaer-Larsen discloses the use of ^{13}C-labelled hyperpolarized compounds for imaging.

First, in the Office Action dated June 16, 2006 ("Office Action"), the Examiner states "it should be noted that the rejections are combination rejections, thus, attacking the references individual[ly] does not overcome the cited prior art rejections." Applicants respectfully submit that it is well-settled law that "the mere fact that it is possible to find

disclosures that might be combined in such a way to produce a new compound does not render such production obvious unless the art also contains something to suggest the desirability of the proposed combination. *In re Bergel and Stock*, 292 F.2d 955. (C.C.P.A. 1961).

In the Office Action, the Examiner clearly does not take into account Applicants Response to the Examiner's Appeal Brief Answer ("Answer") dated December 22, 2005, on page 6, lines 8-12, wherein the Examiner states "Appellant asserts in argument "A" that the references fail to disclose, teach, or suggest all of the elements of the claims. This is not found persuasive because the arguments do not state what element is missing from the combination, but only address the references individually." Applicants respectfully disagree. Through out argument "A" of Applicant's Appeal Brief dated September 23, 2005, Applicants stressed that Felder does not disclose, teach, or suggest materials to be used in the inner surface areas of the vials. Applicants further presented that Schott Glaswerke does not disclose, teach, or suggest diagnostic agents that includes a non-radioactive metal complex or a hyperpolarized material. Additionally, Applicants presented the fact that Walther does not disclose, teach, or suggest diagnostic agents or even contrast agents per se.

Applicant's argumentation was directed to what features the combination of references construed by the Examiner would have. In order to do that, it is perfectly proper to seek to clarify what a single reference actually discloses, since that reads on what the combination would provide. Applicant's have also argued extensively and quoted case law on whether motivation to combine references exists, in the absence of hindsight. This too

clearly addresses the combination. It is therefore factually incorrect that Applicants are only addressing references singly.

Furthermore, on page 6, lines 15-17 of the Examiner's Answer, the Examiner states "almost all pharmaceutical and contrast agents are contained in vials. This is routinely how such pharmaceuticals are stored and sold." Applicants agree with the Examiner that pharmaceuticals and contrast agents are usually stored in vials. One of Applicants arguments on this issue, however, is that there are many and various vial coatings (please see examples below) other than silica that could have equally well been used by Felder in any combination. Additionally, Felder does not even elaborate on the feature of improving a vial. Applicants point out that the word 'vial' is mentioned briefly in Examples 14-19, but the detailed description at Columns 1-8 plus Examples 1-13 and the claims of Felder are all silent on vials. As stated above, Felder is directed to macrocyclic chelating agents and Applicants submit that the focus of Felder, read as a whole (which is how the person skilled in the art would read any prior art reference), is on the preparation of chelating agents, not on a 'teaching' that the agents may be put into a vial. Felder provides no description on the details of the vial, indeed there is no suggestion that the vial is critical or even of any more importance to the invention, it is simply what the solution is stored in. No fair reading of Felder provides a motivation that the vial should be improved to the benefit of the invention. Felder seems wholly satisfied with the vial as it is. That the Examiner has fixated on the vial of Felder suggests to Applicants that the Examiner is simply picking and choosing from Felder only that which will support her position, not what Felder fairly suggests to one of ordinary skill in the art.

Applicants stress that the above arguments read on the lack of motivation to combine Felder with other prior art of record.

On page 7, lines 5-8, the Examiner states "Clearly, the use of silica-coated vials [is] ~~in~~ a known advantage in the field of pharmaceuticals, and therefore one skilled in the art would have been motivated to obtain these benefits for various pharmaceuticals/diagnostic agents, such as, those disclosed by Felder. Therefore, the motivation to combine arises from the benefits of the prior art." Firstly, Applicants point out that the phrase "for various pharmaceuticals/diagnostic agents" is in itself very general and fails to show what specific benefits would be anticipated for the specific diagnostic agents of the present invention, ie. non-radioactive metal complexes or hyperpolarized materials. The lack of a specific perceived benefit or advantage means that it is merely a *possible* benefit amongst many other possible benefits/combinations (see below), which Applicants contend is insufficient motivation to combine. Secondly, Applicants agree with the Examiner that any alleged motivation to combine must arises from the prior art, however, Applicants respectfully submit, however, that there are many other vial coatings that could be used by Felder.

For example, silanizing containers to give clear silicone coatings have been used to prevent aqueous pharmaceuticals from adhering to the inner container walls. Furthermore, inorganic titanium/zirconium oxide coatings have been used in glass bottles to prevent pharmaceuticals and beverages from adhering to the inner walls of the bottle. Also, coatings of silicon, boron, zirconium or titanium nitrides have been used to treat the inner surface wall of a quartz, glass, or ceramic container. Containers internally coated with silicone (ie.

synthetic polymers) used in the manufacture of lyophilized pharmaceutical products have been used as well. These examples demonstrate that the person skilled in the art, without knowledge of the present invention, even if presumed to be motivated to improve Felder by the use of a coated vial, would have been faced with a wide range of possible coatings. Hence, even assuming that person skilled in the art was motivated to improve Felder, the selection and direction of the improvement is far from clear in the absence of hindsight, and could arguably lead towards any of the aforementioned coatings instead of silica.

In light of the aforementioned, Applicants note that the law has long established that "[a] basic mandate inherent in 35 U.S.C. §103 is that "a piecemeal reconstruction of prior art patents in light of the applicants' disclosure" shall not be the basis for a holding of obviousness." *In re Kamm and Young*, 452 F.2d 1052. (C.C.P.A. 1972). Therefore, it would **not** have been obvious to one skilled in the art to modify the compositions disclosed by Felder (i.e., macrocyclic ligands diluted in solution and put into unspecified vials) to use vials having a silica-coating inner surface when there are several other various vial coatings that could be used by Felder.

Furthermore, it is impermissible within the framework of 35 U.S.C. §103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). (emphasis added). Something in the prior art document read as a whole must suggest the desirability, and thus the obviousness, of making the

combination. Uniroyal, *Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1051 (Fed. Cir. 1988). (emphasis added). It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion, or incentive to make the combination made by the inventor. *Northern Telecom Inc. v. Datapoint Corp.*, 908 F.2d 931, 934 (Fed. Cir. 1990). (emphasis added). Applicants respectfully request that the Examiner wholeheartedly take the aforementioned case law in consideration with her reply.

On the bottom of page 3 of the Office Action the Examiner states "while Applicant asserts that the cited prior art uses the generic terms 'diagnostic agent' and hyperpolarized', it is noted that Applicant also uses those generic terms. Applicants respectfully disagree. The term "contrast agent" has a broader meaning than the present invention's term "diagnostic agent" (see above). The term "diagnostic agent" as used in the present invention means either a hyperpolarized material or a non-radioactive metal complex which is in a MRI contrast agent or an X-ray contrast agent. (see page 4 of the specification). A contrast agent, however, can also encompass both non-hyperpolarized and hyperpolarized materials and paramagnetic species which may be metallic (metal ions or metal complexes) or non-metallic, as well as gaseous materials such as fluorocarbons (which are neither hyperpolarized materials nor metal complexes) which function as ultrasound imaging contrast agents, and iodine-substituted aromatics (which are neither hyperpolarized materials nor metal complexes) which are extensively used as X-ray contrast agents.

Additionally, on the bottom of page 3 and the top of page 4 of the Office Action, the Examiner states: "as previously state[d], the broad teaching of the diagnostic agent or pharmaceutical compositions is not viewed as being critical to the advantages of the silica coated vials." Applicants respectfully disagree. Applicants respectfully submit that the specific diagnostic composition as used in the present invention is essential and cannot be broadly construed as suggested by the Examiner. (see page 4 of the specification).

On page 8, lines 11-12 of the Examiner's Answer, the Examiner further states that: "appellant does not assert what specifically in the art provides a teaching away that would lead away from the use of silica-coated vials. It is unclear how 'other improvements' in the art provide a teaching away from the use of silica-coated vials." As indicated in Applicants Appeal Brief dated September 23, 2005, Applicants respectfully submit that the Federal Circuit has determined what constitutes 'teaching away':

A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant [emphasis added].

Para-Ordnance Mfg. v. SGS Importers Int'l, 73 F.3d 1085 (Fed. Cir. 1995).

Applicants respectfully request that the Examiner wholeheartedly take the aforementioned case law in consideration with her reply.

Thus, by teaching positively towards certain embodiments or features as being important or preferred, the art provides a motivation for the person skilled in the art to go in a particular direction. If that direction leads towards subject matter outside the scope of the claims at issue, then it constitutes a 'teaching away'. Applicants maintain that the person skilled in the art, even if assumed to be contemplating improvement of Felder, would focus on the those teachings in Felder of embodiments taught to be important, and be motivated to improve those elements. In Felder those important embodiments and hence potential 'improvements' are clearly the design of the chelating agent, which is described at length at Column 5 line 25 to Column 7 line 65. That constitutes four columns of text. Thus, by applying the *Para-Ordnance Mfg.* decision to Felder, Applicants respectfully submit that the Examiner's logic of seeking to improve the vials, leads in a direction outside the scope of improving the design of the chelating agent, and hence for which no motivation can be found. Felder itself does not even discuss vials or containers, and hence gives no weight to that feature. Felder's emphasis on the chelating agents, and apparent satisfaction with the featureless vial would indicate that improvements to the solution are found by adjusting the formulation of the solution, not by modifying the featureless container. Accordingly, it is clear that based on Felder read as a whole (which is how the Examiner agrees documents should be read), one skilled in the art would not be motivated to seek to improve the vial of Felder.

Applicants stress again that all of the above reads on the combination of Felder with other references, not Felder in isolation.

Furthermore, on page 8, lines 17-18 of the Examiner's Answer, the Examiner states that: "given the disclosure of Felder [should be Schott Glaswerke] of contrast agents and pharmaceuticals in vials, one skilled in the art would be motivated to use silica vials." Applicants respectfully disagree. Applicants again submit that, even if motivation to improve the vial of Schott Glaswerke could be shown, there are several other vial coatings such as silicone coatings, inorganic titanium/zirconium oxide coatings, or coatings of silicon, boron, zirconium or titanium nitrides that could equally well be used as potential improvements of Schott Glaswerke.

Additionally, on page 8, lines 19-21 of the Examiner's Answer, the Examiner states "Appellants assert that unforeseen problems are solved using silica vials. This is not found persuasive because the prior art teaches solving the same problem as discussed in the application." Applicants respectfully disagree with this statement. The prior art does not teach solving the same problems as discussed in the present application. Applicants have stressed that the present invention describes at length how diagnostic agent metal complexes suffer from unforeseen or variable problems which are solved using silica-coated vials. See page 5 line 1 to page 7 line 22 of the present specification. These problems were not recognized in the prior art, and hence the cited references do not suggest applying silica-coated vials to diagnostic agent metal complexes. The solution to the problem provided by the present claims is therefore believed non-obvious over the cited references.

On page 9, lines 7-9 of the Examiner's Answer, the Examiner states: "Appellants also assert that Walther does not limit the coating to silica, but teaches a few possibilities

and there is nothing to point to silica." What Applicants specifically stress is the fact that Walther teaches a wide range of oxide coatings to be used, and that the person skilled in the art would not limit their thinking to merely coating the inner walls of a vial with silica. Therefore, the combination [Felder] + [Walther] in the absence of hindsight ,leads to a wide range of possibilities, not the specific teachings of the present claims. Applicants respectfully again point out it is impermissible within the framework of 35 U.S.C. §103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443 (Fed. Cir. 1986). (emphasis added). Applicants respectfully request that the Examiner wholeheartedly take the aforementioned case law in consideration with her reply.

Furthermore, on page 9, lines 21-24 of the Examiner's Answer, the Examiner states: "Albert does not teach storage of the diagnostic agent in siliconized vials, but teaches storage of the diagnostic agents in a glass vials, see example 3. Nowhere in the cited art is any negative teaching from the use of silica-coated vials for storage of pharmaceuticals, rather only positive teachings are seen in the cited art." Applicants submit that this is another example of the Examiner finding a justification for combining the prior art so as to read on the present invention without regard to what these references, when read as a whole, would

fairly suggest to one of ordinary skill in the art at the time. Albert teaches that silicone should be employed for coating vessels used to store a hyperpolarized gas. One of skill in the art looking at these references would be motivated to follow Albert's specific teachings for preserving the polarization of Albert's own disclosed contrast agent, not the teachings of either Schott Glaswerke or Walther. The Examiner has provided no basis for disposing of Albert's silicone coating in favor of one of the coatings of the secondary references. Once again, the Examiner has used the Applicants' own disclosure as a blueprint for forming an obviousness argument. Since the cited references provide no disclosure, teaching, or suggestion for selecting one of the coatings of the secondary references over the specific coating of the primary reference for use with a hyperpolarized gas, the present invention is patentably distinct thereover.

On page 10, lines 5-6 of the Examiner's Answer, the Examiner questions why Applicants argued over the use of the terms 'silicon', silicone', and 'silica'. Applicants respectfully raised this point to show that the term 'silicon' has long been used for the chemical element silicon (only), and hence this "shorthand" contradicts chemical nomenclature. When the Examiner fails to define what new abbreviations are being adopted, Applicants are disadvantaged in trying to argue their case. Without the use of precise or conventional terminology, applicants cannot be sure whether the Examiner's words are to be given their literal/conventional chemical meaning or not. Since Applicants have silica as an essential feature of their claims, it is clearly of vital importance to establish which terms the Examiner recognizes as interchangeable and which not. The prior examples cited earlier on

silicone (synthetic polymers) makes it even more important that accurate terminology is applied.

Additionally, on page 10, lines 19-20 of the Examiner's Answer, the Examiner states "Schott Glaswerke teaches blood as a specific example, but also teaches the broad use of diagnostic and pharmaceutical agents, see abstract." Applicants again respectfully submit that Schott Glaswerke teaches only blood and blood products as possible diagnostic agents which could benefit from being used in coated vials. Applicants respectfully present that one 'could' combine references is not the standard for making a *prima facie* case of obviousness as such a standard would only grant patentability to combinations which 'could not' be made. Furthermore, a person skilled in the art is unlikely to regard such vials used in Schott Glaswerke as being useful for very different contrast agents such as ^{13}C-labelled hyperpolarized materials as disclosed in Ardenkjaer-Larsen that are not even suggested, disclosed, or taught in Schott Glaswerke.

In view of the remarks hereinabove, Applicants respectfully submit that the instant application, including claims 1-9, is in condition for allowance. Favorable action thereon is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.16(j) or 37 CFR 1.136(a) which may be required, or credit any overpayment, to Deposit Account No. 502-665 in the name of GE Healthcare, Inc.

Respectfully submitted,

/Craig M. Bohlken/
Craig M. Bohlken
Reg. No. 52,628

GE Healthcare, Inc.
101 Carnegie Center
Princeton, NJ 08540
Phone (609) 514-6530
I:\IP\RCE Response after filing Appeal Brief\PZ\PZ9948US RCE (10-16-06).doc